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The long-term prognosis of subendocardial myocardial infarction

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Yale Medical School, 1976
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INTRODUCTION

History of Electrocardiographic Definition of Nontransmural Infarction:

By careful use of electrocardiographic and cardiac enzyme patterns, the spectrum of myocardial infarction can be subdivided into two major forms - the transmural and non-transmural infarctions. However, the second of these forms - the isolated non-transmural or subendocardial infarction - has only been recognized as a distinct clinical entity relatively recently. Barnes and Ball[1] reported the autopsy findings of 49 patients with myocardial infarction and noted that three of these patients had diffuse involvement of the subendocardial area without damage in the outer myocardium. Wilson et. al.[2] in 1935 noted in their pioneer work on the effect of experimental myocardial infarction on the electrocardiogram that infarcts tended to be more extensive in the subendocardium than in the epicardium; and that in marginal areas of the infarct, one often found subendocardial necrosis with viable overlying epicardium. The electrocardiograms recorded from epicardial leads over these marginal areas revealed QR complexes as compared to the classical QS complexes recorded over the transmurally infarcted areas. Therefore it was initially thought by Wilson and others that QR complexes were a sign of non-transmural infarction. In the 1940's several case reports were published describing the clinical histories, pre-mortem electrocardiograms, and autopsy findings of single patients

with isolated subendocardial infarctions, and with these reports the subendocardial infarction became a defined clinical entity.[3-6] All of these early reported cases had pre-mortem electrocardiograms that showed ST segment displacements, usually ST segment depression, and in contrast to Wilson's findings, few showed any alteration of the QRS complex. The autopsy findings showed subendocardial necrosis with generalized atherosclerotic involvement of the coronary arteries, but without the acute occlusions generally associated with classical transmural infarction.

From these early case reports, interest in the subendocardium and subendocardial infarction proceeded in 2 major directions: 1)further clinical-pathological studies of patients found to have subendocardial infarction on autopsy and : 2)experimental work on the effect of subendocardial trauma on the electrocardiogram of experimental animals.

In the early clinical studies most of the interest was also directed at the electrocardiographic changes that were produced by a subendocardial infarction and how these changes were different from those accompanying transmural infarction. Considerable controversy arose as to whether subendocardial infarcts were more commonly associated with ST segment depression alone or with changes in the QRS complex as suggested by Wilson. There was also controversy as to whether any changes at all occurred in the QRS complex in pure subendocardial infarcts and if so how these changes could be explained by standard electro-

cardiographic theory. Levine and Ford[7] published a study of the pre-mortem electrocardiograms of 6 patients discovered at autopsy to have had recent subendocardial infarcts, and Georas et. al.[8] later published a similar study of 17 patients also discovered at autopsy to have had subendocardial infarcts. Both studies found that the most common electrocardiographic manifestations of the subendocardial infarction were ST segment depression over the precordium and lateral limb leads, ST segment elevation in lead avR, and T wave inversions. Neither noted Q wave evolution in these patients. On the other hand, Yu and Stewart[9] and Myers et. al.[10] in similar studies of autopsy-proven cases of subendocardial infarcts found the same ST/T wave changes; however, they also noted frequent alterations of the QRS complex, specifically, abnormal QR patterns, diminution of the R wave in the precordial leads, and less frequently, either notching of the upstroke of the R wave or intraventricular conduction defects of the left bundle branch type. In Myers' study, for example, only one patient of 15 had a normal QRS complex post infarction. Thus, these two studies were more in agreement with Wilson's original theories.

This controversy was somewhat clarified by two further clinical-pathological studies by Cook, Edwards and Pruitt[11,12] of 5 large subendocardial infarcts and 24 small subendocardial infarcts. In both studies the infarcts were acute and associated with demise. In the first report the authors compared 5 extensive subendocardial infarcts involving less

than 50% of the thickness of the myocardial wall with 6 non-transmural infarcts that involved greater than 50% but less than 75% of the myocardial thickness. Only one of the 5 cases with large subendocardial infarcts developed Q waves although the rest had diminution or loss of the R waves in the precordial leads. All 5 of the cases had ST segment depression in the lateral precordial leads and ST segment elevation in lead avR. The non-transmural cases, on the other hand, with involvement of greater than 50% but less then 75% of the myocardial thickness tended to show the classical changes of transmural infarction with ST elevations and deep Q wave evolution. These findings suggested that the subendocardial pattern of ST depression with or without R wave diminution was seen only when the inner half of the ventricular wall was infarcted.

The companion study of the same authors concerned 24 cases of small subendocardial infarcts. In only three of these cases were QRS changes noted, while the large majority showed either symmetrical T wave inversions alone or ST segment depression in the mid or lateral precordial leads. It is of note that in 5 of the patients showing precordial ST segment depression, the infarction was localized on autopsy to the posterior or posterio-septal portions of the heart. The authors concluded that the ST/T changes noted were signs of the intense and sustained ischemia that was responsible for the infarcted tissue but that these changes were not directly caused by the infarction itself. Therefore they suggested that neither

the extent nor localization of the infarct could be predicted from the electrocardiographic changes. They stated, "The very presence of infarcted myocardium is a deduction justified by, but not inherent in, the nature of the electrocardiographic changes...", a statement which still applies to the electrocardiographic diagnosis of subendocardial infarction today. Furthermore, this study by Cook et. al. showed that the most common electrocardiographic manifestations of subendocardial infarction were ST segment depression and T wave inversions especially in the smaller infarcts, but that R wave diminution could occur when the extent of the depth of the infarct approached 50% of the myocardial wall.

At the same time that these clinical studies were being conducted, experimental work directed at the effect of localized subendocardial and epicardial injury on the electrocardiogram in dogs was also being performed in an attempt to further define the contribution of the subendocardium to the electrocardiogram. Again the same controversies arose as in the clinico-pathological studies as to whether the electrocardiographic manifestations of subendocardial necrosis were ST/T wave changes or QRS alterations, and what these changes meant in terms of the electrophysiology of the subendocardium. Pruitt, Barnes and Essex[13] produced subendocardial trauma by applying traction to the inner surface of a dog's heart with a coiled piano wire and found various changes in the QRS complex recorded

in the precordial leads that were similar to those noted by Yu and Stewart in patients; that is, Q wave evolution, notching of the R wave upstroke and diminution of the R wave. They found no changes in the ST segment and "inconstant" T wave changes in these leads. They theorized that the normal epicardial tissue masked any of these latter changes that might be recorded with intracavitary electrodes.

On the other hand, Wolferth et. al[14] produced injury to the subendocardium by curettage and potassium chloride injections and found mainly ST segment displacements with little alteration in the QRS complex as recorded with epicardial leads. It is of note that these authors were able during one experiment to produce negative displacement of the ST segment in the anterior epicardial leads with partial obstruction of the left anterior descending branch of the left coronary artery. Thus they showed that partial decrease in coronary blood flow experimentally could lead to the electrodardiographic changes associated with coronary insufficiency and/or subendocardial infarction. Wolferth theorized that the ST segment depressions recorded with epicardial leads were secondary to positive ST segment displacements occurring at other localizations in the heart - either in the endocardium underlying the epicardial surface from which the recording is performed or in the epicardium of the opposite wall. They did not think that the negative displacements of the ST segment that occurred in epicardial recordings were manifestations of injury or of deprivation

of blood flow at the epicardial portion of the myocardium.

Hellerstein and Katz[15] also studied the effects of subendocardial trauma on epicardial electrocardiographic recordings. They also found that localized subendocardial injury produced ST segment depression with minimal R wave diminution and furthermore, that intracavitary recordings from electrodes next to the injured subendocardium showed ST elevation, thus supporting the postulate of Wolferth et. al. that the ST depression recorded epicardially was a reciprocal effect of injury of the underlying subendocardium. Hellerstein and Katz proposed several electrophysiological explanations for this displacement of the ST segment. They first discussed the concept of injury current at rest, in which they theorized that injured tissue becomes partially depolarized at rest, thereby creating a negative surface potential in relation to uninjured tissue such that current would tend to flow toward the uninjured tissue. This would cause an absolute depression of the TQ segment on recordings of leads near the injured tissue, intracavitary leads in the case of subendocardial injury. During depolarization this injury current would disappear and the ST segment would reach the isoelectric line but would be relatively elevated in relation to the TQ segment. Epicardial leads recording from an area overlying the injured subendocardial tissue would record the opposite deflections - TQ elevations and relative ST depression.

Another explanation offered by Hellerstein and Katz was that the effect of injury was not partial depolarization but unresponsiveness to activation so that at the end of

depolarization, an injury current would exist with the positive potential in the area of the injured tissue due to inability of this tissue to depolarize. In this situation the TQ segment would be isoelectric and the ST segment elevated in recordings adjacent to the injured tissue. Finally Hellerstein and Katz proposed that the electrocardiographic changes of myocardial injury may be secondary to a combination of the above; that is, a partial depolarization of injured tissue at rest as well as unresponsiveness of this tissue during activation. This would lead to opposite displacements of the TQ and ST segments from the isoelectric line that would still appear as St segment elevation on recordings adjacent to the injured tissue and ST segment depression on epicardial recordings in the case of isolated subendocardial damage. In their intracavitary recordings performed during subendocardial injury, Hellerstein and Katz found that all three of these mechanisms were occuring at one point or another.

Samson and Scher[16] agreed that the ST segment shifts noted in myocardial injury were a combination of TQ depression and absolute ST elevation; however, from their research proposed that the mechanism of the ST elevation was not a failure of injured fibers to depolarize but instead was related to earlier repolarization in hypoxic areas. Thus this would also lead to ST segment elevations in intracavitary recordings in the case of isolated subendocardial injury and ST segment depressions in the precordial leads overlying the injured tissue as above.

Although most accepted the hypothesis that the ST segment depression recorded during subendocardial injury and/or infarction were reciprocal effects of the injury currents in the inner myocardium, others such as Prinzmetal et. al.[17] thought that ST depression in precordial leads represented a primary event in the epicardium. Prinzmetal proposed that mathematically the effect of subendocardial injury on the precordial recordings would be slight since the distance between the subendocardium and the chest wall would lead to dissipation of the electrocardiographic changes. His theory was that the ST segment depressions noted on epicardial leads were caused by increased utilization of glucose in hypoxic tissue, which would lead to increased glucose transport into cells and also increased intracellular potassium. This would produce a hyperpolarized resting state that would be recorded as an elevated TQ interval on precordial or epicardial leads as relative ST segment depression.

The controversy as to the electrophysiological mechanism of the ST segment displacements of subendocardial ischemia and/or infarction still exists. More recent studies on the electrocardiographic effects of subendocardial injury produced by direct trauma in one study[18] and by mild to moderate constriction of coronary arteries in another[19] have supported the hypothesis that the ST depression recorded in precordial leads is secondary to injury patterns from the underlying subendocardium. Furthermore, the theories of Hellerstein and Katz still remain accepted as the ones best

explaining the electrophysiological mechanism for the current of injury pattern.[20,21]

Much of the confusion concerning the effect of subendocardial infarction on the QRS complex was clarified by Prinzmetal et. al.[22] in 1954 in a study of the effect of experimentally produced subendocardial infarcts on the electrocardiogram. These investigators studied 7 dogs who had old subendocardial infarcts produced by coronary artery ligation and 12 dogs with acute subendocardial lesions produced by cautery. None of these infarcts led to abnormal Q waves in recordings from precordial or epicardial leads. Prinzmetal et. al. theorized that the subendocardium did not affect the depolarization complex (QRS) of the electrocardiogram and to prove this postulate they performed unipolar intramural recordings from different depths within the myocardium. These recordings showed that the inner third of the myocardium of normal hearts always recorded QS waves and that most of the R wave forces were generated in the outer third of the ventricular wall. Furthermore, with cathode ray oscillograms, they found that the rate of depolarization in the inner ventricular layers was several times faster than that of the outer ventricular layers and therefore, they further proposed that the reason for the lack of contribution of the inner myocardium to the QRS complex was that depolarization occured too rapidly to be recorded on the electrocardiogram. Sodi-Pollares[23] also demonstrated the electrocardiographic silence

of the "electrical endocardial surface" and also attributed it to the fast-conducting Purkinje fibers present in this area of the heart. Furthermore he showed that the thickness of this quickly-conducting layer varied from person to person and from location to location in the heart, being particularly thick in the middle and lower portions of the free left ventricular wall. Thus, it became accepted that pure subendocardial infarcts could electrophysiologically occur without alteration to the QRS complex. Furthermore the electrocardiographic criteria of ST depression without Q wave evolution limited the extent of the infarct to a fairly well defined anatomical portion of the heart that generally included approximately the inner third of the myocardial wall.

Therefore experimental and clinical evidence led to the acceptance of persistent ST segment depression and lack of alteration of the QRS complex as manifestations of the subendocardial infarction.[24] As noted in the studies of Cook, Edwards and Pruitt cited above[12], T wave inversions were also considered to be an electrocardiographic sign of subendocardial infarction. Pruitt, Klakeg and Chapin[25] reported 9 autopsied cases whose electrocardiograms revealed only deep T wave inversions greater than 5 mm. in lead V_3. Eight of these cases had healed subendocardial infarctions discovered on autopsy. The mechanism by which subendocardial injury could be associated with inverted T waves has also been a source of controversy and is still not entirely agreed upon. T waves represent the process of repolarization of myocardium, a process which normally occurs in an epicardial to endocardial direction. Since this is just

opposite to the direction of depolarization, it accounts for the normally upright position of the T wave in the left precordial leads. Inverted T waves in leads in which they are normally upright suggest that the repolarization direction has been reversed so that the epicardium repolarizes later than the endocardium. This could be caused either by earlier repolarization in the endocardium or by later repolarization in the epicardium; and in fact, both mechanisms have been proposed to explain the inverted T wave. As noted before, Samson the Scher showed earlier repolarization in anoxic areas, and this observation has been favored by several authors to explain inverted T waves in the presence of subendocardial injury and/or infarction, in which ischemia would lead to earlier repolarization in the subendocardium.[18] Others have proposed just the opposite - that ischemia leads to retardation of repolarization and therefore predominant subendocardial injury should cause large upright T waves. In fact, Pruitt et. al.[25] have proposed that in developing subendocardial infarction, large upright T waves is one of the very early electrocardiographic changes and that the change to deeply inverted T waves occurs with the necrosis of subendocardial tissue and the extension of the ischemia transmurally. Thus Pruitt et. al. suggested that the inverted T wave was not a direct consequence of subendocardial infarction but instead represented overlying epicardial ischemia. However, they found that statistically, persistent deep inversion of the T waves in a patient with evidence of severe coronary insufficiency was

reliably correlated with underlying subendocardial infarction.

Present Diagnostic Criteria for Subendocardial Infarction:

The present diagnostic criteria used for detecting subendocardial infarctions became complete with the important discovery of the late 1950's that the activity of the cardiac enzymes serum glutamic oxaloacetic transaminase (SGOT) and lactate dehydrogenase (LDH) increased in serum after myocardial necrosis. In 1960 elevations of creatine phosphokinase (CPK) were also found to be associated with myocardial necrosis, and these three enzymes have become established as important criteria in the diagnosis of acute myocardial infarction - either transmural or non-transmural.[26] Furthermore they became especially important in distinguishing subendocardial infarction from persistent subendocardial ischemia without actual myocardial necrosis, since both may have the same electrocardiographic manifestations. Thus the following criteria became accepted for the diagnosis of subendocardial infarction used clinically, in the present study, and in all recent studies of subendocardial or nontransmural infarction:

1) Serum enzyme elevations and curves consistent with acute necrosis of myocardial tissue.

2) Electrocardiographic pattern of ST segment depression and/or symmetrical T wave inversions which tend to persist for days to weeks after the initial episode.

3) Absence of evolution of pathological Q waves.

It should be noted that in this paper the terms "non-transmural" and "subendocardial" are used synonymously. Without autopsy reports it is impossible to differentiate subendocardial necrosis from intramural necrosis involving inner areas of the heart. Furthermore isolated epicardial necrosis is very rare and thus almost all non-transmural infarctions involve these inner areas of the myocardium. The reason for this is discussed later.

One further tool that may prove to be of great use in the future in the diagnosis of subendocardial infarction is that of myocardial scanning, in which radioactive uptake may be indicative of myocardial necrosis. Willerson et. al.[27] performed myocardial scintigrams with technitium 99m stannous pyrophosphate on 88 patients admitted to a coronary care unit with chest pain suggestive of myocardial infarction but with non-transmural electrocardiographic changes. Seventeen of these patients developed enzyme patterns consistent with the presence of acute infarction. All of these patients had positive scans; while the remaining 71 patients who did not develop enzyme changes of infarction all had negative scans. Thus, myocardial imaging may prove useful in the diagnosis of subendocardial infarction especially when enzyme changes are equivocal or obscurred by other concurrent medical problems.

Pathophysiology of Subendocardial Infarction:

Early studies of the effect of the subendocardium on the electrocardiogram seem to indicate that the subendo-

cardium is a distinct part of the myocardium in terms of electrophysiological properties. The fact that isolated subendocardial infarction is now recognized as a fairly common entity, while isolated subepicardial injury is distinctly rare, suggests that the subendocardium is especially prone to ischemia and/or infarction and may also be distinct from the rest of the myocardium in terms of anatomical and mechanical properties as well. Several clinical and experimental observations, for example, show that the subendocardium may undergo acute infarction even in the presence of patent coronary arteries. Autopsy studies of patients with sickle cell trait, profound hypotension, cardiac outflow obstruction, and carbon monoxide poisoning have found frequently isolated subendocardial necrosis and normal coronary arteries.[28,29] Furthermore women with the recently described syndrome of atypical angina, ST/T wave changes on electrocardiogram and patent coronary arteries have also been shown on autopsy to have subendocardial infarctions.[30] Even in patients with documented coronary artery disease an acute coronary occlusion is an infrequent finding on autopsy of patients with only subendocardial infarctions and a frequent finding in patients dying of acute transmural infarctions.[31,32] In a study of post-mortem examinations of patients with acute infarctions, Miller et. al. found that of 49 cases without acute coronary occlusions, 82% had subendocardial infarctions; while of the 94 cases with acute occlusions, 89% had transmural infarctions. Although the significance of acute occlusions

found on autopsy is a controversial subject, the above findings further suggest that the subendocardium is perhaps more sensitive to less degrees of ischemia than the outer portions of the myocardial wall. Experimental studies in support of this hypothesis also exist. For example, the presence of severe anemia, cardiac outflow obstruction and elevated left ventricular end-diastolic pressure produced experimentally in dog hearts have been shown to predispose to subendocardial ischemia and infarction.[33,34] Furthermore decrease in coronary blood flow has also been shown to create a gradient of oxygen supply in the myocardial wall that leaves the subendocardium relatively underperfused and hypoxic.[35]

Thus, several lines of evidence support the contention that the subendocardium is especially prone to ischemia and that it may be anatomically distinct from the remainder of the myocardium in terms of its blood supply and vulnerability. In reference to this Estes et. al.[36] examined carefully on autopsy the coronary arteries of 58 normal human hearts. They found that the intramyocardial branches of the large epicardial coronary arteries were of 2 types: "class A" vessels which branch quickly into a fine network distributed over the outer three-quarters of the myocardium and "class B" vessels that branch infrequently in the outer myocardium and penetrate to the subendocardial layers where they form anastomosing arcades. These arcades coalesce to form a large subendocardial plexus fed by class B vessels at multiple points. It was the hypothesis of these investi-

gators that this subendocardial plexus would supply a potential source of collateral blood flow to the subendocardium in case of occlusive lesions of the main coronary arteries. However, this situation would also make a potentially ischemic focus dependent on these collateral channels, and the flow in these channels, according to Estes, would be determined not only by blood flow in the epicardial arteries but also by the pressure gradient across the myocardial wall. The pressure gradient reflects dynamic forces such as myocardial contractility and ventricular cavity pressure that affect the tissue pressure of the inner myocardium.

Thus the following hemodynamic and anatomical factors are probably important in explaining the vulnerability of the subendocardium:[28,35]

1) Under normal ventricular pressures, the subendocardial fibers are subjected to a greater stretch and develop a greater tension than the outer layers of the myocardial wall. Therefore one would expect increased oxygen requirements for this area and, in fact, one finds the lowest partial pressures of oxygen in the myocardium in the subendocardial tissue.

2) The increased wall tension in the subendocardium during systole causes subendocardial tissue pressures to exceed coronary perfusion pressures so that blood flow to the subendocardium is restricted to diastole.

3) In order to maintain subendocardial blood flow so that it is equivalent to that in other parts of the

myocardium autoregulatory capabilities must be called into action in the subendocardium. It has been calculated that the inner myocardium has a capillary patency of 91% of maximal versus that of 68% in the epicardial area. Therefore under normal conditions there is almost complete utilization of all existing capillaries in the subendocardium so that the ability of the subendocardium to compensate for further ischemia is limited.

Thus these observations suggest that the transmural and non-transmural or subendocardial infarction may possibly occur by different mechanisms - the transmural infarction as a consequence of sudden coronary occlusion with complete cessation of blood flow to the entire wall of the myocardium and the non-transmural infarction as a result of severe ischemia without actually total cessation of blood flow or that only the area most vulnerable to ischemia, the subendocardium, shows necrosis while the better perfused and less vulnerable outer myocardium is spared. In this way the non-transmural infarction may be considered a form of myocardial ischemia intermediate between that of the syndrome of acute coronary insufficiency and that of classical transmural infarction.[26]

Clinical Studies Comparing Transmural and Non-transmural Infarctions:

Historically it was thought that the non-transmural or subendocardial infarction represented a more benign clinical entity than that of transmural infarction with a more favorable clinical course, lower in-hospital mortality, and shorter hospital stay.[37,38,39] In 1960 Edson reported an in-hospital mortality rate of 5.9% for patients with subendocardial infarctions diagnosed by history and electrocardiographic changes but without the use of cardiac enzyme documentation of acute myocardial necrosis.[37] This finding was significantly less than the mortality rate of 28.6% reported by Edson for all patients with acute infarctions of all types studied at the same time. Certainly one must question how many of Edson's patients with "subendocardial" infarctions actually had episodes of persistent angina without infarctions. In 1972 Friedberg, in an introduction to a symposium on myocardial infarction, stated, "In reporting data on acute myocardial infarction there is a tendency to combine the cases of transmural and of subendocardial infarction despite the fact that the clinical course of the latter is generally far more favorable and the incidence of serious complications far lower than in cases of transmural infarction."[39]

Recent studies, however, have challenged this view that the non-transmural patient has a significantly more favorable prognosis than the transmural patient. Abbott and Scheinman[40] divided 230 patients with probable or definite

acute myocardial infarction into 3 groups: 1) definite transmural infarctions - 152 patients with abnormal enzyme curves and the classical electrocardiographic changes of transmural infarctions: ST elevations and pathological Q wave evolution: 2) definite non-transmural infarctions - 45 patients with abnormal enzyme curves, ST segment depressions and/or T wave inversions without the evolution of Q waves; 3) probable non-transmural infarctions - 33 patients who had similar presentations and electrocardiograms as the patients in the definite non-transmural group except that they had only "minimal" enzyme elevations. They found that there were no significant differences between the 3 groups in terms of pre-infarction history of angina, infarction, hypertension or diabetes. Furthermore there were also no significant differences in post-infarction incidence of ventricular premature contractions or of the malignant arrhythmias including ventricular tachycardia or fibrillation. The transmural patients and definite non-transmural patients had comparable incidences of cardiogenic shock (18% transmural and 22% non-transmural) and comparable mortality rates (19% transmural and 37% non-transmural), both of which were significantly greater than that of the probable non-transmural group (shock 3%, mortality 3%). These authors concluded that the mortality rate and prognosis of these acute infarction patients was better correlated with the magnitude of enzyme rise than with electrocardiographic changes. Furthermore, they concluded that patients with minimal enzyme eleva-

tions and electrocardiographic changes of non-transmural infarction had a significantly better in-hospital course than the others but that their risk of arrhythmic death, as judged by the incidence of ventricular ectopy was equally as great.

In a companion study the same authors subdivided their above groups of definite and probable non-transmural patients into 3 groups each, with the following electrocardiographic changes as criteria:[41] 1) ST segment depression with or without T wave inversions, 2) T wave inversions alone and 3) ST segment elevations without Q wave evolution. They found that the group with definitely abnormal enzyme elevations and ST segment depressions had a significantly higher mortality rate than the other groups. This higher mortality rate for patients with subendocardial infarctions and ST depression versus those with only T wave inversions was also noted by Lown et. al.[42] In Abbott and Scheinman's study 15 patients had definitely abnormal enzyme curves and only T wave inversions on electrocardiogram and these patients had a mortality rate of 20%, significantly greater than the 0% mortality rate found for a similar group in Lown's study. The patients with ST depressions and definitely abnormal enzyme curves had a mortality rate of 47%. Post-mortem examinations of 6 of these patients revealed evidence of recent and old transmural infarctions. Four of these cases had electrocardiographic changes that correctly localized the area of acute infarction but on autopsy all of these cases proved to have

acute transmural infarctions and evidence of old infarctions as well. The authors proposed that the absence of classical transmural changes was due to a cancelling of electrical events because of the presence of transmural infarction on opposite sides of the myocardium.

In reviewing Abbott and Scheinman's work, one is particularly struck by two somewhat surprising findings: 1) the very high mortality rate of patients with "definite" non-transmural infarction (37%) and 2) the finding on autopsy of patients with acute infarctions and electrocardiographic changes consistent with non-transmural infarctions of recent transmural infarctions in all cases. The mortality rate reported in this study for non-transmural infarction patients is much higher than that found in similar studies of transmural and non-transmural patients that will be discussed later. The actual mortality rate reported for non-transmural infarctions is affected by the division of these patients into the two categories of probable and definite infarction with the distinction between the two groups being whether the peak enzyme elevation was twice that of the lowest recorded value. For all their possible or definite non-transmural patients the mortality rate was 23%. Furthermore the autopsy findings of transmural infarctions suggests that some of these patients may have ultimately developed Q waves if they had survived their infarction. Two of the 6 autopsied cases with ST segment depression died within 24 hours post-infarction and five died within 6 days. Perhaps the high mortality rate for non-transmural infarction

patients, especially those with ST segment depressions in this study was caused by the inclusion of patients with acute transmural infarctions who had either old transmural infarctions that mask the electrocardiographic changes or early non-transmural infarcts followed by transmural extension that was not recorded. The results do, however, make uncertain the electrocardiographic reading of acute non-transmural infarcts in the face of prior infarctions.

Medias et. al.[43] also compared the in-hospital course of patients with transmural and non-transmural infarctions as defined by enzyme elevations and electrocardiographic changes similar to those used in the above study. They studied 104 patients - 61 post-transmural infarction and 43 post-non-transmural infarction. No significant difference was found between the two groups in prevalence of type of arrhythmias occurring post-infarct, in incidence of cardiogenic shock, or in in-hospital mortality (9.8% transmural and 9.3% non-transmural). The transmural patients did have a significantly higher incidence of congestive heart failure post infarction (33% transmural and 10% non-transmural, $p<.02$) and significantly higher enzyme elevations (average peak SGOT: 288 transmural and 130 non-transmural). It is of note that all four of their patients who had fatal non-transmural infarctions had had a prior infarction while only one of the six with fatal transmural infarctions had a prior infarction. They did not report autopsy findings. It was concluded in this paper that the prognosis of patients post infarction could not be correlated

with the type of infarction.

The third major study comparing the in-hospital course of patients after transmural and non-transmural infarctions was conducted by Rigo et. al.[44] They studied 111 patients with transmural infarctions and 49 patients with non-transmural infarctions with hemodynamic monitoring by Swan Ganz catheters within 24 hours of acute infarction. The non-transmural patients were divided into 2 groups: 1) 26 patients whose serial electrocardiograms showed ST/T wave changes and normal QRS complexes and 2) 22 patients whose electrocardiograms revealed abnormalities in the QRS complex that were probably old such as intraventricular conduction defects, poor R wave progression, or Q waves related to previous infarctions, but without changes of an acute transmural infarction. The transmural patients were found in this study to have significantly higher cardiac enzyme elevations than the combined non-transmural group (average peak SGOT: 189 transmural and 53 non-transmural) and there was no significant difference in enzyme elevations between the two non-transmural subgroups. All three groups had similar incidences of arrhythmias and of congestive heart failure. The mortality rates were 22% for the transmural patients and 13% for the total non-transmural group, which was also not a significant difference; however, the non-transmural patients with no QRS abnormalities had a 0% in-hospital mortality rate versus 27% for the non-transmural group with changes in their QRS complex, which was statistically significant with $p<.05$. Hemodynamically

this former group had a significantly higher left ventricular ejection fraction and a lower left ventricular filling pressure than those patients with transmural infarctions. The authors concluded that this non-transmural group with no old abnormalities in their QRS complex possibly represented a subgroup of infarction patients with a better in-hospital prognosis.

Rigo et. al. also followed up through 20 months those patients discharged post infarction and found that, although one group of non-transmural patients had a lower mortality rate in-hospital, after discharge there was no significant difference in late mortality between the three groups. The mortality rates at 20 months were 18% for patients post non-transmural infarction without QRS abnormalities, 14% for patients post non-transmural infarction with the QRS abnormalities described above, and 18% for patients post transmural infarctions. The authors did not report the causes of death in these cases but proposed that the non-transmural patients might be prone to fatal arrhythmias post discharge.

It is of note that the study by Rigo et. al. is the only one in the literature that specifically compares the long-term prognosis of patients post transmural and non-transmural infarctions. Norris et. al.[45] did report a three-year follow-up study on 530 patients discharged post-acute infarction. The main goal of this study was to identify the factors that were relevant to long-term prognosis. It is noted somewhat peripherally in this study that the patients in this group that had subendocardial infarctions

had a three-year mortality rate of 32% which was comparable to that of patients after transmural infarctions. However the criteria used in making the diagnosis of subendocardial infarction are not described in the paper nor is the significance of the finding of comparable mortality rates for these two types of infarction elaborated upon, except that type of infarction was not one of the factors included in those thought to affect prognosis.

Several other authors have proposed, like Rigo et. al. that patients post non-transmural infarctions are particularly prone to fatal arrhythmias and sudden death;[34,46,47] however, this hypothesis has never been examined in any clinical study. It is the purpose of the present study to compare the in-hospital and post-discharge clinical courses of patients post transmural and non-transmural infarctions in order to detect any differences in short-term and long-term prognosis and also to document the relative frequencies of the various causes of death post discharge. In this way it is believed that the non-transmural infarction can be better defined as a clinical entity and the treatment of patients post non-transmural infarctions can be more effectively planned.

MATERIALS AND METHODS

The hospital records of 418 consecutive patients admitted to Yale-New Haven Hospital between January 1 and December 31, 1971, with a diagnosis of possible or definite myocardial infarction (MI) were reviewed. Of these patients, 219 were determined to have sustained an acute myocardial infarction by the following criteria:
(1) A history of chest pain thought to be ischemic in etiology and occurring within 48 hours prior to admission.
(2) Serum enzyme elevations consistent with an acute MI, specifically an increase in serum glutamic oxaloacetic transaminase (SGOT) to a level above normal limits (10-35 units) with a peak value at least 100% higher than the lowest recorded initial value. Patients with associated medical conditions that might explain an elevated SGOT were excluded. All patients also had a parallel increase in creatine phosphokinase (CPK) and in lactic dehydrogenase (LDH) levels, although less rigid criteria were applied to the interpretation of these values.

Patients meeting the criteria for acute MI were divided into two groups according to electrocardiographic (ECG) changes noted upon hospitalization:
(1) Transmural Myocardial Infarction (TMI): 148 patients whose serial ECGs showed acute ST segment elevations $\geq$1 mm. with subsequent evolution of pathological Q waves $\geq$1 mm. in depth and at least 0.04 seconds in duration.
(2) Non-Transmural Myocardial Infarction (NTMI): 40 pa-

tients whose serial ECGs showed either only persistent ischemic changes - either ST segment depression $\geq$ 1 mm. (with or without symmetrical T wave inversions) or symmetrical T wave inversion alone. Q waves did not evolve in these patients. These changes were considered secondary to acute ischemia and could not be explained by digitalis effect, left ventricular hypertrophy, electrolyte disturbances, or by any other condition similarly causing ST/T wave changes. The ECGs of a representative patient from the NTMI group are shown in Figures 1-4 to demonstrate the typical ECG changes noted.

The remaining 31 patients of the 219 fulfilling the criteria for acute MI were excluded from the study for the following reasons: 3 patients had non-atherosclerotic heart disease causing the ECG and enzyme changes and 28 patients presented serial ECGs which could not be classified with certainty into either the TMI or NTMI group because of either equivocal ECG changes not consistent with the strict criteria for either group or because of conduction disturbances that prevented accurate ECG reading.

Daily enzyme determinations, daily 12-lead ECGs and recordings of all dysrhythmias were available for all patients for their stay in the coronary care unit. Enzymes and ECGs were also obtained after the CCU stay but not as frequently. The patients' records were reviewed to document pre-infarction clinical status, in-hospital complications post infarction, and time and cause of death

if applicable.

To examine the post-discharge course of the 161 patients surviving hospitalization, intensive effort was made to contact each patient's private physician. Information sought included cardiac status in terms of angina, congestive heart failure and re-infarction, any ECG changes occurring post discharge, cardiac catheterization data and occurrence of bypass surgery if performed, and date and circumstances of death if patient had expired. For those patients who had not been followed post discharge by a private physician, telephone contact was made directly with the patient or with his family if the patient had expired. Follow-up information was obtained on 155 of the 161 patients: 119 (96%) of the 124 TMI patients and 36 (97%) of the 37 NTMI patients. The mean follow-up period for all patients was 36 months but extended to at least 40 months for those patients still alive at the end of the follow-up period. Patients discharged who expired during the follow-up period were classified into three groups according to the cause of death:

(1) Sudden death: Death occurring within one hour after the onset of cardiac symptoms and before hospital admission.

(2) Other cardiac death: Death known to occur after hospital admission for acute myocardial infarction, intractable congestive heart failure or any other cardiac disease.

(3) Death from non-cardiac causes.

The Chi-square method was used for statistical analysis

of the data; p values of less than 0.05 were considered significant.

RESULTS

Pre-Admission History:

A comparison of the pre-infarction clinical histories of the TMI and NTMI patients is shown in Table 1. The average patient age and male-to-female ratio were similar in the two groups. There was also no significant difference between the two patient groups in the incidence of a history of previous infarction, congestive heart failure, hypertension or diabetes. The NTMI patients did have a significantly higher incidence of previous angina (85% for NTMI patients versus 61.5% for TMI patients, $p < .01$)

In-Hospital Course:

As noted previously, the electrocardiographic changes shown by NTMI patients were ST segment depression and/or T wave inversions. The relative frequency of these changes and their localization are shown in Table 2. The most common pattern was ST segment depression in the anterior-lateral precordial leads alone with or without accompanying T wave inversion. This pattern was noted in 22 or 55% of the NTMI patients. Ten or 25% of the NTMI patients had similar ECG changes in both the anterior and inferior leads together. Only 1 case (2.5%) had these changes in the inferior leads only. The remaining 7 patients (17.5%) had ECGs which demonstrated only T wave inversions and these were almost exactly equally divided between those having these changes in the anterior leads only, those with the

changes in the inferior leads only, and those in both anterior and inferior leads.

The electrocardiographic changes of NTMI persisted for at least 24 hours in all 40 patients and for at least four days in 38 (95%) of the patients. These changes tended to resolve gradually during hospitalization with the ST segments generally reverting to normal before the T waves if both were present in a patient. However, only four patients had complete return of the ECG to pre-infarction status by discharge. Of the 33 patients with ST segment depression on admission ECG, 12 had resolution of this change by discharge, while only 4 of the 33 patients with abnormal T wave inversions on admission ECG had return of these T waves to an upright status by discharge.

The electrodardiographic changes accepted as diagnostic for acute transmural infarction were the classical ST segment elevations and Q wave evolution. An approximately equal number of the TMI patients showed these changes in the anterior leads alone and in the inferior leads alone. Fourteen patients (9%) showed new Qs in both the anterior and inferior leads.

The average peaks of SGOT, LDH, and CPK for the TMI and NTMI patients are shown in Table 3. Cardiac enzyme elevations were on the average significantly higher ($p<0.01$) in the TMI group than in the NTMI group with peak levels for the TMI patients being almost twice that of the peak levels of the NTMI patients.

The two groups were also compared for the usual complications of infarction: Congestive heart failure, dysrhythmias, atrioventricular block, distal conduction defects, cardiogenic shock and mortality. As shown in Tables 3 and 4, all of these complications tended to be more common in the TMI group; however, statistical significance was achieved only by the difference in the incidence of ventricular tachycardia (17.5% TMI patients versus 2.5% NTMI patients, $p<0.02$), in the incidence of accelerated idioventricular tachycardia (18% TMI versus 5% NTMI, $p<0.02$) and in the incidence of one or more forms of atrioventricular block (25.7% TMI versus 10% NTMI, $p<0.05$). 6.8% of the TMI patients experienced primary ventricular fibrillation as compared to none of the NTMI patients and cardiogenic shock occurred in 8% of the TMI patients and 2.5% of the NTMI patients. Neither of these differences achieved statistical significance. In-hospital mortality was 16.8% for the TMI group and 7.5% for the NTMI group, also a statistically insignificant difference. The most common causes of death were cardiogenic shock and lethal dysrhythmias which accounted for two-thirds of the mortality of both groups.

Post-Discharge Course:

Of the 161 patients surviving the index 1971 infarction and discharged from the hospital, follow-up information was obtained on 119 TMI patients and 36 NTMI patients. The post-discharge course of the TMI and NTMI groups is shown in Table 6. Only 53% of the NTMI patients discharged were still

alive at the end of the follow-up period which extended for at least 40 months post-infarction for all patients. This survival rate is in comparison to the 70% survival shown by the TMI patients discharged during the same period. This difference achieved statistical significance with a p value of < 0.05. An analysis of the causes of death in both groups revealed that the apparent reason for this poor survival in the NTMI group appeared to be the high incidence of sudden death occurring in these patients. Of the NTMI patients discharged post-1971 infarction, 33% experienced sudden death during the follow-up period, as compared to 15% of the TMI deaths post-discharge. The incidence of death from other cardiac causes, including intractable heart failure and documented re-infarction, was similar in the two groups (9.2% TMI and 8.3% NTMI), as was the incidence of death from non-cardiac causes (5.9% TMI and 5.6% NTMI). The cumulative mortality, a figure including both in-hospital deaths immediately after index infarction as well as deaths occurring in the follow-up period, was 51% for the NTMI patients and 42% for the TMI patients, a difference which was not statistically significant.

Figure 5 shows in actuarial form the survival curves for the two groups post-discharge after 1971 infarction. Patients dying from non-cardiac causes were excluded from this graph; therefore, if one assumes that the sudden deaths in both groups were cardiac in etiology, then the decline in slope of both the TMI and NTMI survival curves in this graph is secondary solely to cardiac-related mortality. As

noted, the two populations followed a comparable course through 24 months; however, by 40 months the NTMI patients showed a cardiac-related mortality of 41% versus 23% for TMI patients, a statistically significant difference with $p<0.05$. The average interval between discharge and death for those patients expiring during this period post discharge was 15.8 months for the TMI patients and 21.6 months for the NTMI patients.

A comparison of the cardiovascular status of the 83 TMI patients and of the 19 NTMI patients still alive at the end of the follow-up period is shown in Table 7. There was no significant difference between the two groups in terms of incidence of congestive heart failure or of recurrent infarction; however, the NTMI patients did have a significantly higher incidence of recurrent angina.

An attempt was made to identify those factors in the patients' clinical histories and hospital courses that were associated with an unfavorable post-discharge prognosis. As shown in Table 8, each factor was examined separately for its effect on patients with TMI and NTMI by comparing the mortality of patients who presented with or developed the stated factor with patients who lacked the factor. For the TMI patients in this study the following seemed to be statistically correlated with an increase in post-discharge cardiac mortality: a history of cardiac symptoms prior to admission of greater than five years, a history of congestive heart failure prior to admission, the presence of persistent congestive heart failure in

hospital post-infarction, and finally, involvement of the anterior myocardial wall as indicated by diagnostic MI changes in the anterior precordial leads on ECG. For the NTMI patients, these factors could not be shown to have a statistically significant effect on post-discharge prognosis, at least partially because of the smaller number of patients involved. It is notable that the post-discharge mortality of the NTMI patients whose ECGs demonstrated ST segment depressions in the anterior precordial leads was 50% as compared to the 12.5% post-discharge mortality of those patients whose ECGs showed only T wave inversions or ST depression limited to the inferior leads. This difference did not achieve significance when analyzed statistically; however, when one examines the entire NTMI group including the three patients who expired in the hospital, one finds a cumulative mortality, including post-discharge and in-hospital deaths, of 54.8% for the patients with anterior precordial ST segment depression on ECG as compared to a cumulative mortality of 12.5% for those NTMI patients with only T wave inversions or ST depression only in inferior leads, a difference that does achieve statistical significance with a p value of <0.05.

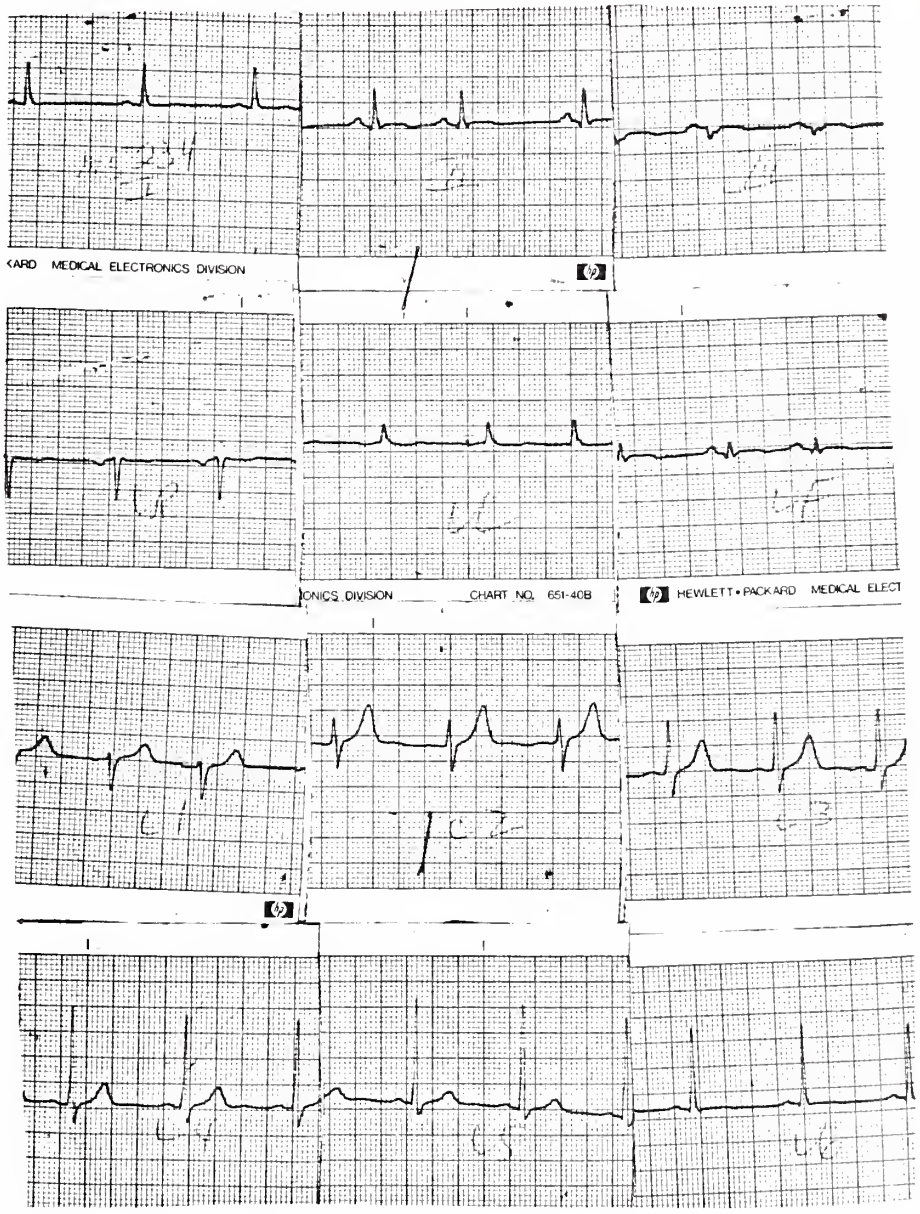
The following factors could not be statistically demonstrated in this study to be associated with a significantly poorer post-discharge course for either the NTMI or TMI patients: history of previous angina, history of previous infarction, history of hypertension, high enzyme elevations, or the occurrence of ventricular premature

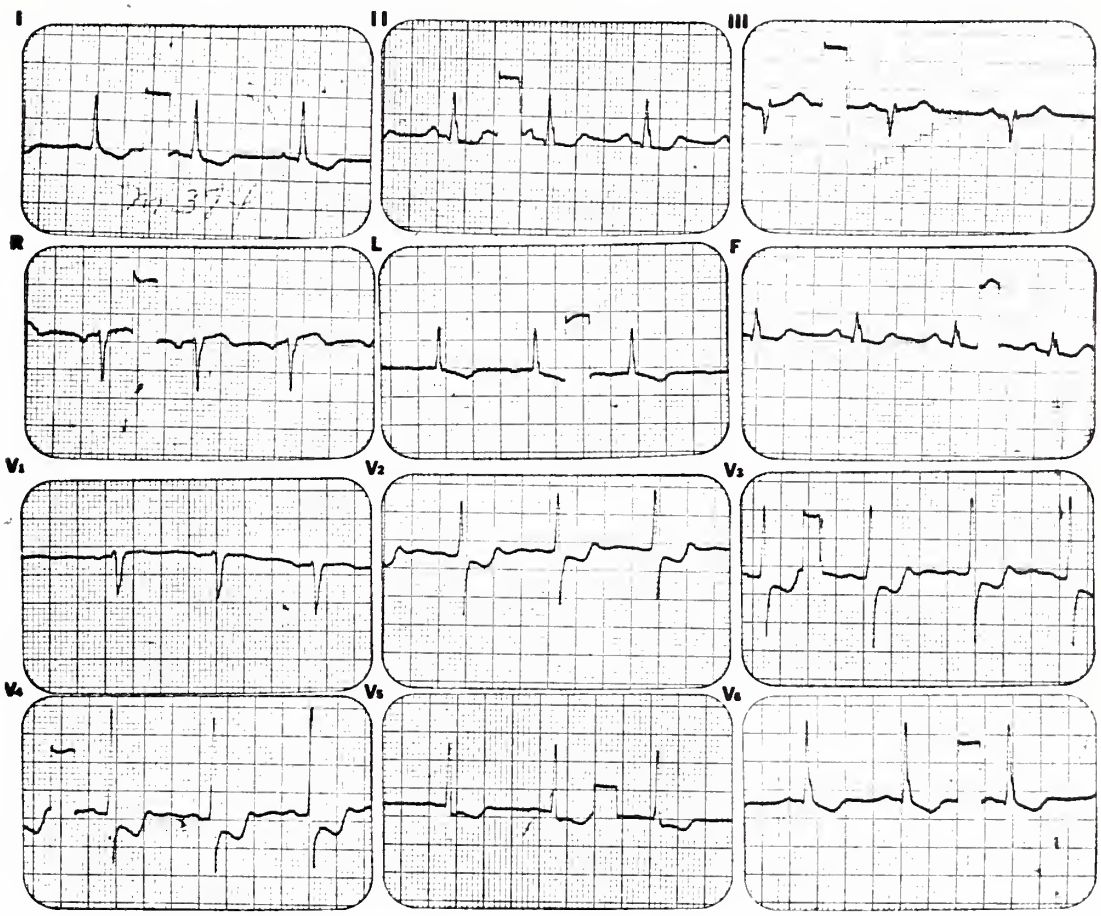
contractions recorded in the CCU.

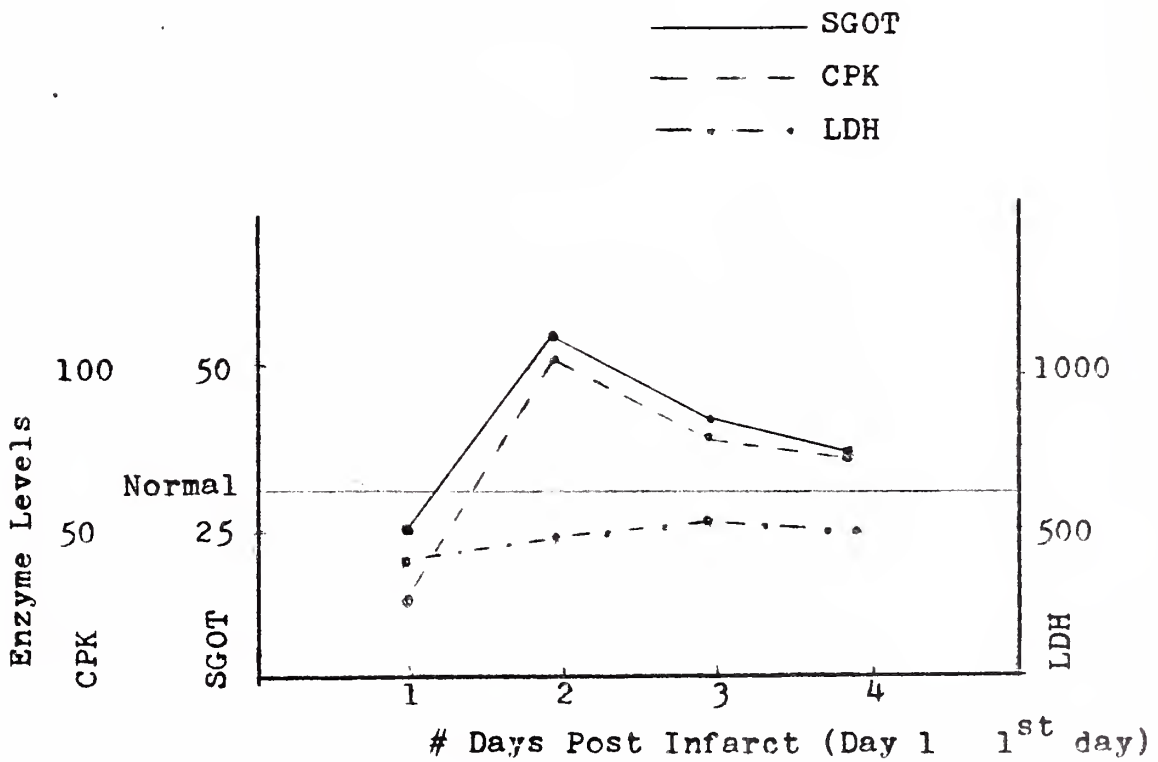
In Table 2 one notes that a higher percentage of the NTMI patients than TMI patients had ECG changes involving the anterior leads. According to the standard electrocardiographic interpretations, this finding suggests that a higher percentage of the NTMI patients had anterior infarctions although Cook et. al. have noted that localization of a non-transmural infarct by ECG changes can be misleading. In any event it has been suggested in Table 8 that anterior ECG changes are associated with a less favorable prognosis in this study for both TMI and NTMI patients. Therefore in Table 9 the in-hospital and post-discharge mortality of the TMI and NTMI patients with ECG changes in their anterior precordial leads is compared. The anterior NTMI patients and anterior TMI patients did not have a very different in-hospital mortality from the entire NTMI and TMI group; however, some differences are noted in the post-discharge mortality. For the discharged anterior TMI patients the mortality during the follow-up period was 40% as compared to 30% for the entire TMI group; while that of the anterior NTMI patients was 52% versus 47% for the entire NTMI group. On comparing the anterior NTMI patients, one notes that the post-discharge mortality and incidence of sudden death is still higher in the NTMI group although the difference no longer achieves statistical significance.

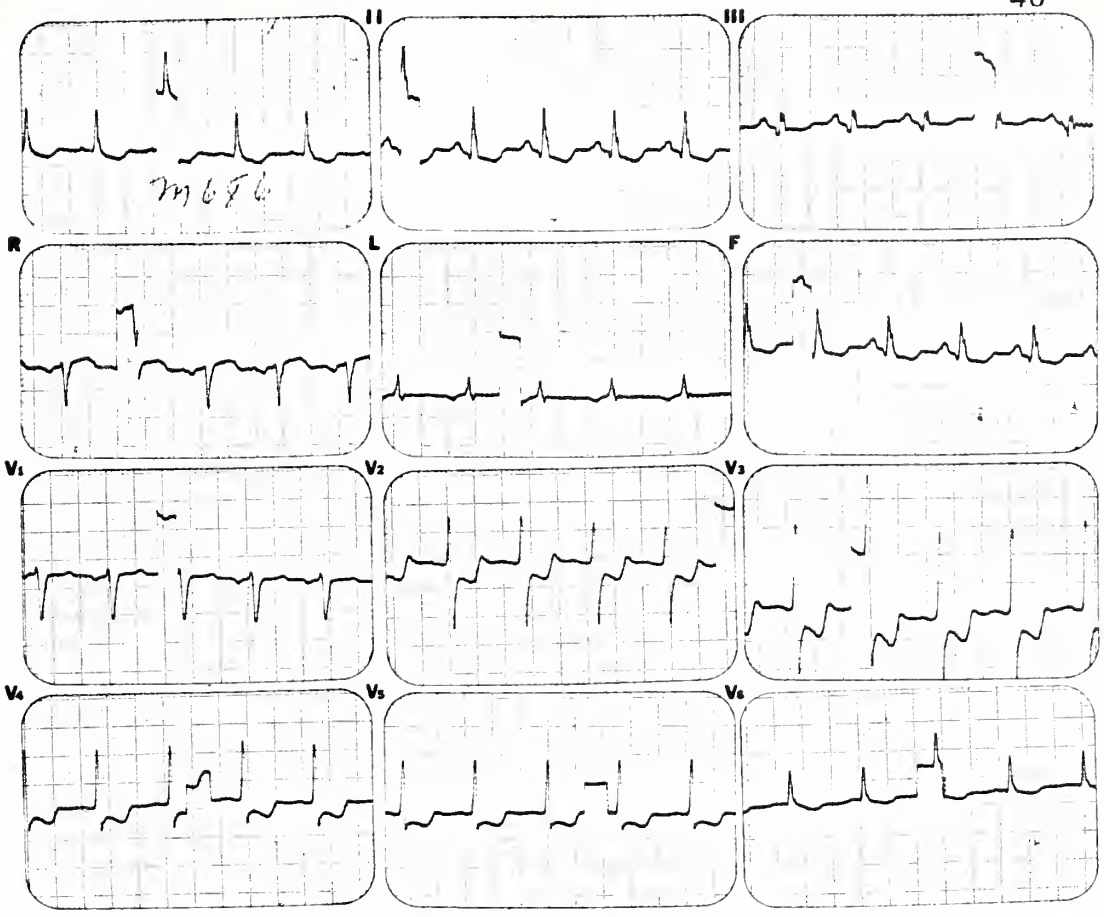
The following four electrocardiograms are those of a 62 year-old white male with a past history of an inferior wall infarction in 1969. ECG #1 is from 1/1970 and shows small q waves in II,III, and avF consistent with old inferior wall infarction. This patient was admitted on 10/3/71 with increasing angina at rest for 24 hours and ECG #2 which shows ST depression in II and V_{2-5} and T inversion in I,avL and V_{5-6}. Cardiac enzyme elevations were consistent with acute infarction as shown in graph. ECG #3 from day 7 of hospitalization shows persistence of ischemic changes without evolution of new Q waves. ECG #4 from day 22 shows return of electrocardiogram to baseline. ECGs and enzymes were consistent with a diagnosis of acute subendocardial infarction.

ECG #1

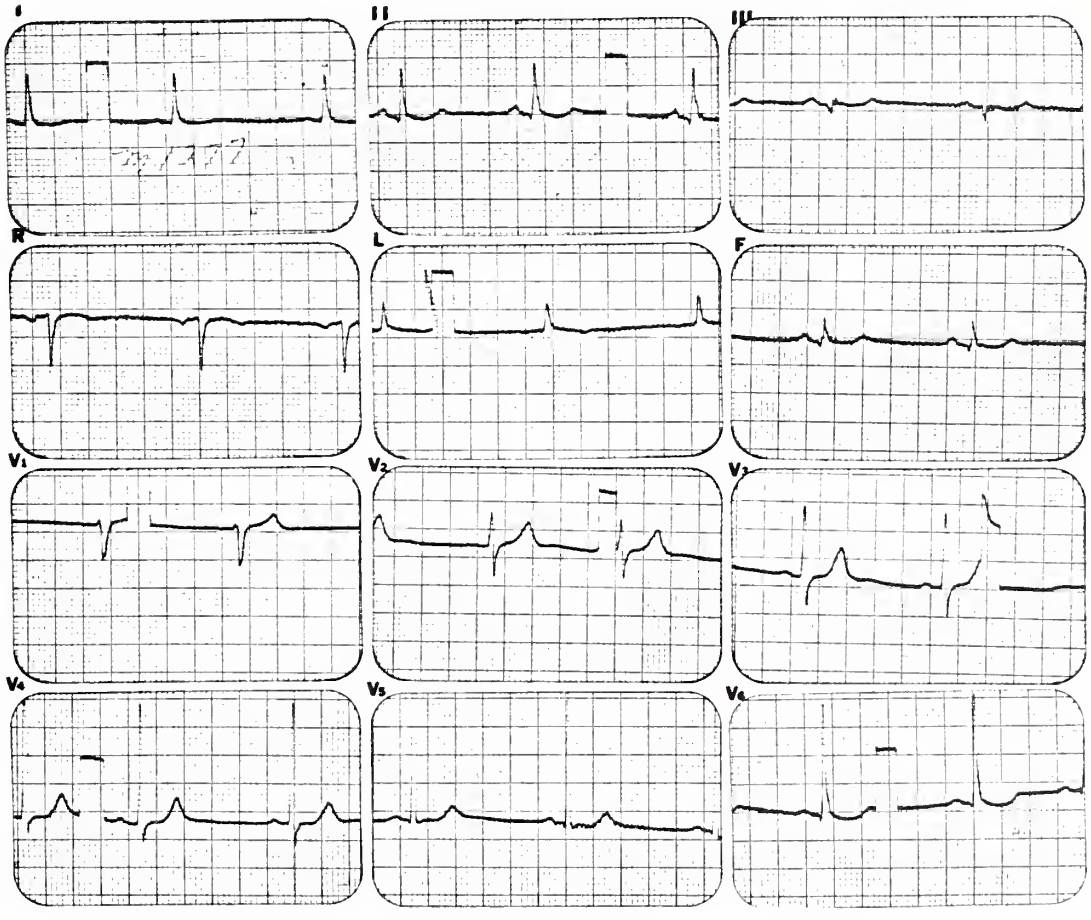



I
II
III
R
L
F
V1
V2
V3
V4
V5
V6


SGOT
CPK
LDH
Enzyme Levels
100
50
Normal
50
25
CPK
SGOT
1000
500
LDH
1
2
3
4
Days Post Infarct (Day 1 1st day)

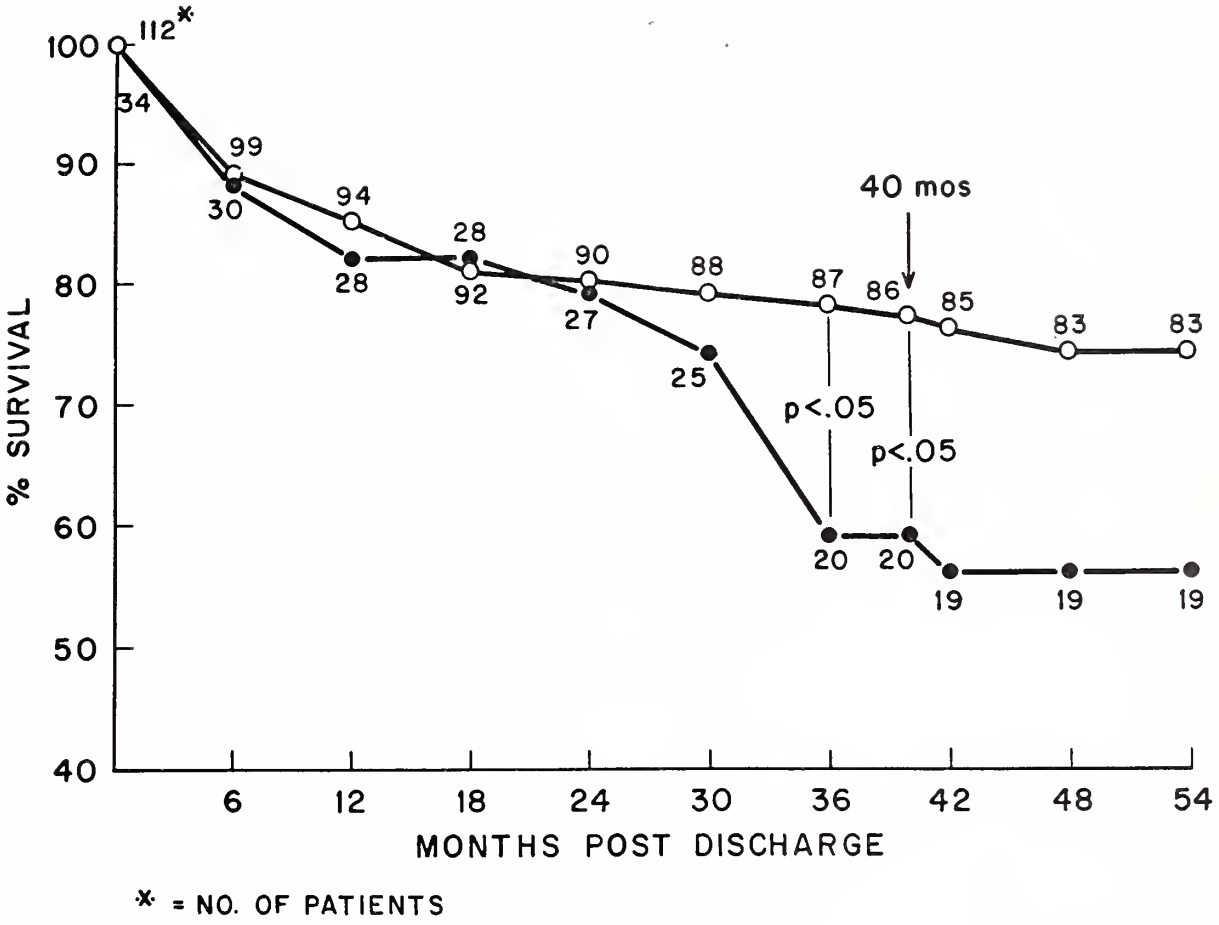


ECG #3



ECG #4

FIGURE 5



This actuarial plot displays the post discharge course of TMI patients (open circles) and NTMI patients (closed circles). Shown on the ordinate is the per cent of patients alive while the abscissa shows number of months post discharge after index infarction of 1971. Patients dying during the follow-up period of non-cardiac related deaths were not used in determining this graph. The two populations follow a comparable course through 24 months; marked differences in survival are noted at 36 months, achieving statistical significance at the p .05 level.

Table 1: Pre-Admission History

	TMI	NTMI	p
Number of Patients	148	40	
Average Age	60	63	NS
Sex - Number of Males	117 (72%)	28 (70%)	NS
History of Previous Angina	91 (62%)	34 (85%)	<.01
History of Previous MI	37 (25%)	13 (32.5%)	NS
History of Congestive Heart Failure	34 (23%)	15 (37.5%)	NS
History of Hypertension	47 (32%)	9 (22.5%)	NS
History of Diabetes	25 (17%)	7 (17.5%)	NS

Table 2: Enzyme Elevations

	TMI	NTMI	p
Average peak SGOT (normal: 15-35 units)	222	119	<.01
Average peak LDH (normal: 200-600 units)	1663	980	<.01
Average peak CPK (normal 5-50 units male 5-30 units female)	297	157	<.01

Table 3 : Electrocardiographic Localization of Infarction

A) ECG Localization of TMI:

Anterior-Lateral only (V_1-V_6,I,L)	Inferior only (II,III,F)	Both
66 (45%)	68 (46%)	14 (9%)

B) ECG Manifestations of NTMI:

	Anterior-Lateral Leads Only	Inferior Leads Only	Both	Total
ST depression with T wave inversion	16	1	9	26 (65%)
ST depression only	6	0	1	7 (17.5%)
T wave inversion only	3	2	2	7 (17.5%)
ST elevation avR				18 (45%)

Table 4: Complications Post MI

	TMI	NTMI	p
Sinus Tachycardia	70 (47%)	17 (41.5%)	NS
Sinus Bradycardia	49 (33%)	7 (17%)	NS
Ventricular Premature Contractions	82 (55.4%)	24 (60%)	NS
Atrial Fibrillation	19 (12.8%)	3 (7.5%)	NS
Atrial Flutter	9 (6.0%)	2 (5%)	NS
Ventricular Tachycardia	25 (17.0%)	1 (2.5%)	<.02
Accelerated Idioventricular Rhythm	16 (18.0%)	2 (5%)	<.02
Ventricular Fibrillation	10 (6.8%)	0 (0%)	NS
Asystole	4 (3.0%)	1 (2.5%)	NS
Atrioventricular Block:			
First-degree	24 (16.2%)	3 (7.5%)	
Second-degree	4 (2.7%)	0 (0.0%)	
Third-degree	10 (6.8%)	1 (2.5%)	
Total	38 (24.3%)	4 (10.0%)	<.05
Distal Conduction Defects:			
RBBB	16 (10.8%)	0	
LBBB	11 (7.4%)	2 (5.0%)	
LAHB	22 (14.8%)	5 (12.5%)	
LPHB	2 (1.3%)	0	
Total # Cases with Defects	36 (24.3%)	7 (17.5%)	NS

Table 5: Complications Post MI

	TMI	NTMI	p
Congestive Heart Failure*	106 (71.6%)	26 (65.0%)	NS
Moderate to Severe Congestive Heart Failure≠	68 (45.9%)	13 (32.5%)	NS
Cardiogenic Shock@	12 (8.1%)	1 (2.5%)	NS
Mortality	24 (16.8%)	3 (7.5%)	NS

* Rales at lung bases, S_3, or X-ray findings of vascular redistribution or Kerley B lines

≠ Persistent failure or pulmonary edema requiring treatment with digitalis or diuretics

@ Drop in blood pressure to less than 90 mm. systolic with cyanosis and/or change in mental status. Pressors were given.

Table 6: Post-Discharge Course

	TMI	NTMI	p
Discharged from Hospital	124	37	
Contacted for Follow-up	119	36	
Alive	83 (69.8%)	19 (52.8%)	<.05
Sudden Death	18 (15.1%)	12 (33.3%)	<.02
Other Cardiac Death	11 (9.2%)	3 (8.3%)	NS
Non-Cardiac Death	7 (5.9%)	2 (5.6%)	NS
Cumulative Mortality (Includes In-Hospital and all Post-Discharge Deaths)	60/143 (42%)	20/39 (51.3%)	NS

Table 7: Cardiovascular Status of Patients Alive at the End of the Follow-up Period

	TMI	NTMI	p
Patients Alive	83	19*	
Angina Present at Some Time	53 (63.8%)	15 (83%)	$<.05$
Angina $\geq$Class II@	30 (36.2%)	11 (61%)	$<.05$
Congestive Heart Failure	39 (47.6%)	7 (39%)	NS
Recurrent MI	10 (12%)	5 (26%)	NS

* One patient was known to be alive and without recurrent MI; however, other information about angina, CHF could not be obtained.

@ New York Heart Association Classification - angina occurring regularly with strenuous exertion. Criteria added in this study for class II angina was that it occur at least once a month.

Table 8: Relationship of Historical Data and In-Hospital Course to Post-Discharge Cardiac Mortality

	NTMI			TMI		
	Present	Not Present	p	Present	Not Present	p
Historical:						
Age greater than 60	*4/14 (29%)	11/22 (50%)	NS	15/47 (32%)	14/72 (19%)	NS
Previous Angina Class II	10/24 (42%)	5/12 (42%)	NS	16/50 (32%)	14/69 (19%)	NS
Previous MI	5/13 (39%)	10/23 (43%)	NS	9/27 (33%)	27/92 (22%)	NS
Previous CHF	6/14 (43%)	9/32 (28%)	NS	11/20 (55%)	18/99 (18%)	<.01
Previous Hypertension	4/9 (44%)	11/27 (41%)	NS	11/41 (27%)	18/78 (23%)	NS
5 year history of cardiac symptoms prior to MI	6/16 (38%)	9/20 (45%)	NS	8/17 (47%)	21/102 (20%)	<.05
In-Hospital:						
Persistent CHF post MI	6/9 (67%)	9/27 (33%)	<0.1	19/45 (42%)	10/74 (14%)	<.01
Peak SGOT 100	8/16 (50%)	7/20 (35%)	NS			
Peak SGOT 200				13/58 (22%)	16/61 (26%)	NS
VPCs in CCU	9/21 (43%)	6/15 (40%)	NS	17/60 (28%)	12/59 (20%)	NS
Primary ST changes in anterior leads on ECG (depression for NTMI; elevation for TMI)	14/28 (50%)	1/8 (12.5%)	<0.1	20/62 (32%)	9/57 (16%)	<.05

*Denominator indicates no. patients with (or without) stated factor; numerator no. post-discharge deaths among these patients. Calculated mortality rate is noted in parentheses.

Table 9: Anterior Transmural Infarction Compared to Anterior Nontransmural Infarction

	Ant. TMI	Ant. NTMI	p
In-Hospital:			
Number	76	37	
Mortality (in-hospital)	14 (18%)	3 (8%)	NS
Post-Discharge:			
Discharged from Hospital	62	34	
Contacted for Follow-up	58	33	
Mortality (post-discharge)	23 (40%)	17 (52%)	NS
Sudden Death	12 (21%)	12 (36%)	NS
Other Cardiac Death	8 (14%)	3 (9%)	NS
Non-Cardiac Death	3 (6%)	2 (6%)	NS
Cumulative Mortality (Includes in-hosptial and post-discharge)	37 (51%)	20 (56%)	NS

DISCUSSION

These data suggest that patients post non-transmural myocardial infarctions have a generally guarded prognosis post-discharge with a high cardiac mortality rate, high incidence of sudden death and high incidence of recurrent angina. The in-hospital data comparing patients post-transmural and non-transmural infarctions in this study seem to indicate that the NTMI patient does not have a significantly better in-hospital course, although there were two complications that did in this study occur significantly more frequently in the TMI group: ventricular tachycardia and atrioventricular block. The mortality rates were not significantly different. These results, in general, are in agreement with the recent studies comparing TMI and NTMI patients of Madias et. al.[43] and Rigo et. al.[44] The former study found a higher incidence of congestive heart failure in the TMI patients and both reported higher enzyme elevations in the TMI group, as was noted in the present study. However, in both studies the mortality rates of the two groups of patients were not significantly different. Rigo reported a mortality rate of 22% for his TMI patients versus 13% for the NTMI patients, a result very comparable to that of this study in which the mortality rates were 17% TMI and 8% NTMI. Thus there does not seem to be strong support for the concept that patients post-NTMI have a significantly more favorable in-hospital course than patients post-TMI.

The post-discharge findings are also interesting in that they appear to show an actually poorer prognosis for those patients who survive non-transmural infarctions as compared to those surviving transmural infarctions. The mortality rates found during the 40-month follow-up period were 47% for the NTMI patients discharged post-index infarction and 30% for the TMI patients ($p<0.05$). Furthermore, the NTMI patients demonstrated an increased incidence of sudden death that was more than twice that of the TMI group (33% versus 15%, $p<0.05$). As noted previously, the only other study to compare directly the post-discharge course of patients after NTMI and TMI is that of Rigo et. al. who found comparable mortality rates for the two groups through 20 months. Although they theorized that the NTMI patients were prone to fatal arrhythmias post-discharge, they did not report the causes of death of the patients.

As shown in figure 1, the TMI and NTMI patients in this study also had comparable mortality rates through 24 months; however, by 36 months the NTMI mortality was significantly greater than that of the TMI patients. The reason for this late separation of survival curves is not altogether clear. One could suggest that the transmural infarction with the greater degree of myocardial necrosis would lead to an unstable condition in the period of time immediately following infarction that would become less dangerous as scar tissue was formed and collateral circulation was developed. As suggested previously the non-transmural infarction probably represents an acute episode of

coronary insufficiency without actual arterial occlusion in which enough ischemia occurs to cause some necrosis of the more vulnerable portions of the myocardium such as the subendocardium. In some cases this amount of damage would be enough to precipitate a fatal arrhythmia or cardiogenic shock in the immediate post-infarction period. For the other NTMI patients since coronary occlusion presumably had not occurred, a predisposition for severe ischemia would remain with the potential for sudden fatal arrhythmias. Thus, one might not expect to find the same leveling off of the mortality curve with time that one sees with the TMI patients.

The overall mortality rate in this study, including both in-hospital and post-discharge deaths was 42% for TMI patients and 51% for NTMI patients, (p not significant), at 40 months post-index infarction. These findings therefore suggest that the prognosis of patients post-NTMI is probably at least as poor as for patients post-TMI; furthermore, for those patients surviving the infarction, the long-term prognosis may indeed be less favorable for patients with NTMI.

In this study there was also an attempt to identify factors in the pre-infarction history and post-infarction hospital course that might be possibly predictive of post-discharge prognosis. For the TMI patients several general factors such as duration of symptoms of cardiac disease, previous history of congestive heart failure, anterior wall involvement on electrocardiogram, and the presence of post-

infarction congestive heart failure did prove to have a significant effect on prognosis of those patients discharged. In the NTMI group the small number of patients prevented any statistical identification of similar factors affecting prognosis. It is of interest that those patients with ST segment depression in the anterior leads had a significantly poorer prognosis than those patients with either solely T wave inversions or ST/T wave changes limited to the inferior leads. Lown,[42] in a general coronary care study, found a similar discrepancy between the in-hospital courses of patients with non-transmural infarctions showing ST segment changes versus only T wave inversions on admission electrocardiograms. In Lown's study the 50 NTMI patients with ECGs showing only T wave inversions had an in-hospital mortality rate of 0% versus and in-hospital mortality rate of 28% for those NTMI patients with ST wave changes. The study did not examine post-discharge prognosis of these patients.

It was somewhat surprising that even with the high incidence of post-discharge sudden death presumably secondary to fatal arrhythmias in both groups, especially the NTMI patients, that no correlation could be shown between the occurrence of ventricular ectopy post-infarction and the latter occurrence of sudden death or even cardiac mortality. Both Chiang et. al.[48] in a study of a community of over 5,000 individuals and Kotler et. al.[49] in a study of 160 patients, all at least 3 months post-infarction, found that significant ventricular ectopy was associated with a

definite increase in the incidence of sudden death. Vismara et. al.[50] in a recent study found that only ventricular arrhythmias occurring late in the in-hospital course were of value in predicting sudden death while those occurring in the CCU were not. The ventricular ectopy described in our study was only from the CCU. Late in-hospital arrhythmias and ectopy post-discharge were not examined and this may well explain the lack of correlation in our study between ectopy and sudden death, especially in light of the above studies. Certainly these patients with the high incidence of sudden death should have more frequent ECG examination during hospitalization post-CCU and also as outpatients post-discharge.

Before comparing the data from this study to the other natural history studies in the literature, one must be aware of some of the pitfalls in such a retrospective study. This was a survey of all the acute infarctions admitted to one institution in a single year. The patients were not necessarily experiencing their first cardiac event; in fact, many had had previous infarctions and in this way they are not a heterogeneous group. Since the study was a chart review and retrospective follow-up, differing amounts of information were available for each patient. Furthermore angiographic data were available for only a few of the patients either from cardiac catheterization or autopsies to determine the extent of coronary artery disease in the two groups of patients. However,

these problems exist with many of the natural history studies and if one is cautious in interpreting these data in light of these variables, there are still some inferences that can be made concerning the nature and possible therapy of non-transmural infarctions by comparing these results to the other studies of coronary artery disease in the literature.

Several previous studies have been directed at the prognosis of patients surviving myocardial infarctions. Several of these involve patients with their first documented infarction. For example, Pell and D'Alonzo[51] followed 1331 employees of the Du Pont Co. for at least five years after their first infarction. 336, or 25.2%, of these patients died within the first 24 hours post-infarction and 399 (31.5%) died within the first 30 days. Those patients surviving 30 days were followed through five years and had a mortality rate of 26% over this period. The authors found that the long-term prognosis of these patients was affected by the presence of hypertension and increased age. Pell and D'Allonzo also reviewed nine other studies examining the five year survival of patients post-infarction, some of which included patients with previous infarctions, and found that the 5-year mortality rate averaged 35%. On the other hand, Juerghans et. al.[52] from Mayo Clinic found a more substantial 5-year mortality rate of 45% in 224 patients after first documented infarction.

Probably more comparable to the present study are those papers examining the long-term prognosis of all patients

post-infarction including patients with histories of previous infarctions. Norris[45] in a three-year study of 530 patients post-infarction found a mortality rate over this period of time of 33% for all patients including those with previous infarctions and, as stated earlier, patients with subendocardial infarctions. Four factors were identified which seemed to decrease prognosis - age, heart size, presence of pulmonary congestion and a history of previous ischemic event. Rosenberg[53] studied 131 survivors of myocardial infarction and arrived at a three-year mortality rate of 43% and a five-year mortality rate of 49%. It was further noted that a history of previous infarction significantly affected prognosis as patients with previous infarcts had a mortality rate over five years of 72% versus 38% for those without such a previous history.

The 40-month mortality rates in our study of 30% for TMI patients and 47% for NTMI patients are in general agreement with the above studies. It is difficult to explain the discrepancy between the 32% mortality of Norris for NTMI patients and the one in our study; however, it is difficult to compare the two studies since Norris was not specifically examining non-transmural infarctions and makes no mention of the criteria used in the diagnosis. It is of note that while in Rosenberg's and Norris' studies a history of previous infarction adversely affected prognosis, such a history did not have a significant effect on the long-term mortality rates of either the TMI or NTMI patients in our study.

The prognosis of patients post-non-transmural infarctions should also be compared with that of patients after an episode of acute coronary insufficiency since by clinical and electrocardiographic standards the two groups are very similar. In fact, the only criterion clearly separating these two types of ischemic events is the development of cardiac enzyme elevations with the NTMI, indicative of severe enough ischemia to cause myocardial necrosis. Thus, the non-transmural infarction can be viewed as occupying an intermediate position in the spectrum of acute ischemic heart disease between that of the transmural infarction and that of acute coronary insufficiency or pre-infarction angina. It shares with the transmural infarction the development of actual myocardial necrosis and shares with coronary insufficiency the tendency to affect primarily the subendocardium and also probably the lack of complete coronary occlusion.

Gazes et. al.[54] followed 140 patients with pre-infarction angina for 10 years to determine their natural history. The mortality rates for these patients was 31% at three years, 39% at five years and 52% at 10 years. A high risk group was also defined as those patients who continued to have ischemic pain despite maximal medical therapy. This group showed a mortality rate at three and five years of 63% and 73%. This is in comparison with the total three-year mortality rate for the NTMI patients in our study, including in-hospital and post-discharge deaths, or 51% which is much greater than that of the average pre-infarction angina patient in

Gazes' study but less than that of his high risk patients.

In a study by Krauss et. al.[55] of 100 patients with acute coronary insufficiency, the one-year mortality rate was 15%. These patients were followed for a total of 20 months and showed an overall mortality over this period of 27% and a cardiac-related mortality of 22%. 60% of the cardiac deaths were sudden. In our non-transmural study, the mortality from all causes for the first 20 months post-infarction was 26% with a cardiac related mortality of 23%. 56% of the cardiac deaths were sudden. Thus a comparison of the results of Gazes and Krauss with the non-transmural results seem to point out a close similarity at least prognostically between the non-transmural infarction and the syndrome of acute coronary insufficiency, as one might theoretically expect.

One problem of the present study and of the other natural history studies cited is that little data is available on the degree of coronary disease in these patients. The results of the Framingham study in which 5127 patients with all forms of arteriosclerotic cardiovascular disease were followed for eight years showed that the survival of patients who presented with uncomplicated angina was similar to that of patients who first presented with transmural infarction.[56] This finding suggests that it may not be the manifestation of coronary artery disease that determines prognosis but the degree of progression which may or may not be associated with actual infarction.

Several recent studies of long-term prognosis of patients with angiographically documented coronary artery disease have confirmed this hypothesis. Oberman et. al.[57] performed cardiac catheterization on 246 patients between 1965 and 1970 and followed them for a mean of 22 months. The analysis of their results determined only two factors to be independently correlated with subsequent prognosis: the presence of cardiac failure and the severity of the coronary artery disease in terms of number of vessels involved. Other factors, specifically electrocardiographic evidence of previous infarction, history of angina, hypercholesterolemia and hypertension, were not found to have any effect independent of their relationship to these two factors.

Reeves et. al.[58] has reviewed a number of these studies on the relationship of single, double and triple vessel disease to subsequent prognosis. From these studies he arrived at the following average annual mortality rates: single vessel disease - 2.2% per year; double vessel disease - 6.8% per year; and triple vessel disease - 11.4% per year. Later studies by Bruschke et. al.[59] and Burggraf and Parker[60] are in agreement with these figures. Burggraf and Parker noted no significant correlation between a history of angina or of infarction and subsequent survival. Thus, these studies suggest that the main determinants of prognosis in ischemic heart disease are the severity of the coronary artery disease and possibly the presence of con-

gestive heart failure. Since the NTMI patients in this study had a poor prognosis post-discharge with a mortality of 47% over three years, one might infer that this is evidence for the presence of severe coronary disease, probably involving all vessels, in these patients. Only one study has been directed at the severity of coronary artery disease in patients with non-transmural infarctions. Madigan et. al.[61] performed early coronary angiography on 32 patients after non-transmural infarctions and demonstrated that 97% had anatomically severe disease (>75% stenosis) in at least one or more artery and that 67% had significant involvement of two or more vessels. This finding apparently confirms that the NTMI is a manifestation of advanced coronary artery disease. Furthermore, one sees the importance of angiographic data in performing studies on the natural history of the various forms of ischemic heart disease.

Because of the unfavorable natural history of patients post-non-transmural infarctions and the high incidence of sudden death in these patients, possible therepeutic modalities should be considered. The high incidence of sudden death, in most cases presumably secondary to fatal arrhythmias, raises the controversial question of the use of anti-arrhythmic prophylaxis in this setting. As noted earlier, studies by Chiang et. al. and Kotler et. al. have shown that electrocardiographic recording of ventricular ectopy in normal individuals and post-infarction patients is correlated with a significantly increased incidence of sudden death. It has been suggested that anti-arrhythmics such as

procaineamide and quinidine might be effective in decreasing the incidence of ventricular extrasystoles when used on an outpatient basis,[62] although there is significant strong opposition to even this hypothesis.[63] However, it has not been unequivocably demonstrated that these drugs can decrease the incidence of sudden death when used as prophylactic long-term therapy. Kosowsky et. al.[64] did find a slight but not statistically significant decrease in the incidence of sudden death in 39 procaineamide-treated patients versus 39 control patients followed for three months post-acute infarction. The treated patients had a 2.6% incidence of sudden death during this time as compared to 10.2% for the non-treated control patients. Interestingly there was no difference between the treated and untreated patients in terms of occurrence of ventricular extrasystoles; however, the treated patients did have a significantly reduced incidence of ventricular tachycardia and coupled extrasystoles.

The major problem with the use of the presently available drugs for long-term prophylaxis versus sudden death is the high incidence of toxicity of these drugs. In Kosowsky's study the treated patients received 1.5 to 2.0 grams of procaineamide as their daily dose and reactions to the medication, including fevers, rashes and headaches, forced discontinuance of the drug in the first three months of therapy. Twelve of the 26 patients treated for three months or longer developed lupus-like reactions with a rise in ANA titer in all but one of these patients. Only eight of the initial 39 patients continued the procaineamide for greater than 18

months and all of these patients had elevations in their ANA titers. Thus, procaineamide, the most effective of the present commonly used oral anti-arrhythmics according to Koch-Weser, does not seem to be acceptable for long-term use. Jelinek et. al.[65] found that 1.2 to 1.8 grams per day of quinidine orally was effective in suppressing ventricular ectopy in 7 of 23 patients (30%) with frequent ventricular extrasystoles; however, significant toxicity developed in 11 (48%) of these patients. Dilantin is another anti-arrhythmic that may have use as prophylaxis; however, it appears to be less effective than procaineamide or quinidine although it may be less toxic.[62,63] The important point is that the presently available oral anti-arrhythmics are probably not the solution to the problem of how to provide long-term prophylaxis against sudden death to high risk patients since they have not been shown to be unequivocably effective when used in this regard and the incidence of unacceptable toxicity is high when they are administered to a patient over a long period of time. However, in light of the new, less toxic anti-arrhythmics that are being developed and again the high incidence of sudden fatal arrhythmias in NTMI patients, one might suggest that randomized studies are indicated to examine the effect of these drugs in this setting.

The other therapy that may be of possible benefit to patients post-non-transmural infarctions is that of coronary artery bypass surgery. Theoretically these patients

have viable myocardium beyond the infarcted subendocardium that may well be prone to future ischemia. In this situation bypass surgery could possibly re-establish adequate blood flow to this tissue. While most studies indicate that revascularization procedures are effective in reducing the frequency and severity of angina, there is much controversy as to their effect on patient survival.[66,67,68] Sheldon et. al.[69] studied the survival post-op of 1000 patients receiving bypass grafts and found an annual mortality of 9.3% per year. Problems with this study are: 1) it was not a randomized prospective study comparing patients evaluated at the same time; 2) the average mortality rate of 9.3% per year for the medically treated group seems high for a group of single, double and triple vessel patients if one uses the cumulated mortality figures of Reeves et. al.

McNeer[70] compared a group of 378 surgically treated patients with a "comparable" group of 407 medically treated patients and found that survival was the same in both groups at two years, although twice as many surgical patients had relief of angina. McNeer did, on the other hand, identify a subgroup of patients - those with three-vessel disease, normal arteriovenous O_2 difference and abnormal left ventriculogram - who had a significantly higher survival rate when treated surgically than when treated medically. In general, it is presently believed by the majority of investigators in this area that patients with two and especially three-vessel disease may have a better survival with surgical therapy,[68,69] although further studies are certainly

needed to demonstrate this more definitely.

How do these data apply to the patient with a non-transmural infarction? As stated earlier, in the catheterization study of Madigan et. al.[61] of 32 patients post-NTMI, 21 (66%) demonstrated at least 75% stenosis of two or three of the major coronary arteries. Of these 21 patients, 15 were considered acceptable candidates for bypass surgery. Therefore, in light of the very poor prognosis that these NTMI patients showed in our study and the severity of coronary artery disease found in these patients by Madigan et. al., we suggest that a well-controlled, prospective study is indicated to determine the effect of coronary artery bypass surgery on the survival of these patients.

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